PATENT
SYN-0044

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Johannes PLATTEEUW et al.	:	
Serial No.: 10/824,619	:	Group Art Unit: 1618
Confirm. No.: 6264	:	Examiner: Susan T. TRAN
Filed: April 15, 2004	:	

For:

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed April 1, 2008, and the Petition for a two month extension of time submitted concurrently herewith, appellants hereby submit the Appeal Brief in connection with the above-identified application. Entry and consideration of this Brief are requested. For the reasons set forth hereinafter, reversal of each of the Examiner's rejections is respectfully requested.

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I. Real Party in Interest

The real party in interest is Synthon IP Inc., a corporation of Virginia, which is one of several privately held companies ultimately owned by Synthon Holding BV, a corporation of The Netherlands.

II. Related Appeals and Interferences

There are no appeals or interferences, previously or currently, that are related to this application.

III. Status of Claims

Claims 1, 5, 7-9 and 11-37 are pending in the application, wherein:

Claims 1, 5, 7-9 and 11-37 are rejected.

Accordingly, claims 1, 5, 7-9 and 11-37 (all claims) are subject to this appeal.

IV. Status of Amendments

No amendments to the claims were made subsequent to the Final Rejection. Accordingly, the claims on appeal remain unchanged from the Final Rejection.

V. Summary of Claimed Subject Matter

The present invention relates to the surprising discovery that silicified microcrystalline cellulose can be used to provide an orally disintegrable tablet. This

discovery is expressed in each of the independent claims by reciting that: (a) the tablet contains at least 50% of silicified microcrystalline cellulose and (b) the tablet disintegrates within 1-15 seconds (or in "15 seconds or less" in claim 34). Each independent claim and its antecedent support in the specification are summarized below.

Independent claim 1 recites a tablet for oral administration that comprises an effective amount of an active agent and at least 50% silicified microcrystalline cellulose. The tablet is also "orally disintegratable within the range of 1 to 15 seconds." The term "orally disintegratable" as defined in the specification refers to disintegration "measured by the *in vitro* disintegration test described in US Pharmacopoeia 701, without disks" (specification at page 6, lines 16-18). The *in vitro* testing is a reasonable model for the oral experience in that "[g]enerally, though not necessarily, the *in vitro* time is somewhat longer than the orally experienced time for disintegration" (specification at page 6, lines 20-22). Support for the combination of an active and silicified microcrystalline cellulose as well as the "at least 50%" of silicified microcrystalline cellulose can be found on page 4, lines 19-21, of the present specification. Support for the meaning/definition of silicified microcrystalline cellulose can be found on page 7, line 15, through page 8, line 8, of the present specification. Likewise the definition of the term "orally disintegratable" is set forth beginning on page 6, line 16, through page 7, line 6, while the claimed time range is set forth at page 7, line 12. .

Independent claim 30 recites an orally disintegratable tablet that "consists essentially of" (1) 50-90% silicified microcrystalline cellulose, (2) 0-20% low substituted HPC, (3) a lubricant, and (4) and effective amount of a pharmaceutical active agent. Additionally the tablet exhibits disintegration within 1 to 15 seconds in an *in vitro*

disintegration test. Support for the HPC and lubricant can be found on page 8, line 9, through page 9, line 6, of the present specification (noting linc 15 for "0-20%" and line 19 for L-HPC). See also page 14 for a preferred tablet recipe that corresponds to claim 30.

Independent claim 32 recites a process which comprises disintegrating a tablet having at least 50% of a matrix of silicified microcrystalline cellulose and an active agent, by placing the tablet in a water environment for 1 to 15 seconds. Support for process is set forth on page 17, lines 10-15, while the time frame of 1-15 seconds is provided on page 7, lines 10-13, especially line 12.

Independent claim 34 is a Jepson claim wherein an orally disintegrating tablet that disintegrates in 15 seconds or less is improved by using a matrix of silicified microcrystalline cellulose in an amount of at least 50% in the tablet. Support can be found on page 5, lines 12-13; page 6, lines 2-5; and original claim 34.

VI. Grounds of Rejection to be Reviewed on Appeal

Whether claims 1-5, 7-9, 11-20, 22-34, 36 and 37 are unpatentable under 35 U.S.C. §103(a) over Shimizu (U.S. Patent No. 6,328,994) in view of Sherwood (U.S. Patent No. 5,585,115).

Whether claims 1, 5, 7-9, and 11-37 are unpatentable under 35 U.S.C. §103(a) over Betzing (U.S. Patent No. 5,776,492) in view of Shimizu and Sherwood.

VII. Arguments

A. §103(a) Rejection over Shimizu in view of Sherwood

Claims 1-5, 7-9, 11-20, 22-34, 36 and 37 stand rejected as being unpatentable under 35 U.S.C. §103(a) over Shimizu et al., U.S. Patent No. 6,328,994 (hereinafter "Shimizu") in view of Sherwood et al., U.S. Patent No. 5,585,115 (hereinafter "Sherwood"). This rejection fails to establish a prima facie case of obviousness and reversal thereof is requested.

1. The Applied Art

Shimizu relates to orally disintegratable tablets. The tablets are comprised of fine enteric-coated granules containing at least 10% drug and an "additive." (Shimizu at col. 5, lines 51-56). The additive typically contains a water-soluble sugar alcohol (Shimizu at col. 9, lines 49-67), which provides strength "and sufficient disintegration or dissolution in the oral cavity" (Shimizu at col. 10, lines 1-6). The additive may also contain microcrystalline cellulose ("MCC") as a binder in order to provide "a solid preparation which exhibits more excellent strength of a preparation while retaining excellent

disintegration and dissolution in the oral cavity" (Shimizu at col. 11, lines 43-51). No mention is found, however, of applicants' claimed silicified microcrystalline cellulose.

The amount of the MCC additive, when present, is described as "about 3 to 50 weight % ... relative to 100 weight % of the orally disintegrable tablet ***apart from the fine granules***" (emphasis added) (Shimizu at col. 10, lines 25-29). Thus, up to "50%" of the "additive" can be MCC. Because the tablet is not 100% "additive," the maximum amount of MCC is necessarily less than 50% of the tablet. The amount of additive in the tablet is not specifically defined in Shimizu and the Examiner has not identified any amount or proportion. Nonetheless, the working examples teach that tablets contain about 38% to 48% of the drug-containing fine granules and, correspondingly, 62-52% of "additive." For instance, Example 4 at col. 26, lines 17-28, shows that in 250g of a tablet blend[1], 120g was the fine granules; meaning 52% of the tablet is "additive" and 48% is granules. Under this teaching, the maximum amount of MCC (i.e., 50% of the additive) is approximately 26-31% of the total tablet weight (i.e., half of 52-62%). This maximum amount of MCC is well below the claimed "at least 50%" of silicified MCC.[2]

Also Shimizu generically teaches an oral disintegration time of preferably "one minute or less" down to "more preferably about 30 seconds or less," (Shimizu at col. 12, lines 42-47). The working examples, however, achieved oral disintegration in 20 to 35 seconds; which is longer than the applicants' claimed 1-15 seconds.

The secondary reference, Sherwood, is directed to a silicified microcrystalline cellulose ("silicified MCC") excipient as called for in the applicants' claimed invention.

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[1] the total weight is the sum of 120 + 87.75 + 8.5 + 4.5 + 19.5 + 6.5 + 1.3 + 1.3 + 0.65 = 250

[2] In practice, the Shimizu Examples use low amounts of MCC based on the total tablet weight; using at most 11.5% crystalline cellulose and more typically (i.e., six examples) in the range of 5.25-9% crystalline cellulose. Two Examples did not use any MCC additive.

The silicified MCC has superior compressibility over conventional MCC (Sherwood title; col. 4, lines 38-41; col. 6, lines 11-30; and col. 11, lines 38-46). According to Sherwood, improved compressibility enables the use of less excipient (see col. 3 lines 23-40) and, in the context of wet granulation, the amount of silicified MCC can be "substantially reduced" relative to the amount of conventional MCC (col. 12, lines 9-13). Sherwood does not teach or suggest an orally disintegratable tablet. Likewise, Sherwood does not ascribe any improvement in disintegration or attaining the function of providing oral disintegration to silicified MCC. The amount of silicified MCC to be used in a formulation is not limited; however, the amount of conventional MCC is taught to be typically 5-30% or more (Sherwood at col. 7, lines 48-51).

Sherwood demonstrates the advantage of compressibility of silicified MCC in, *inter alia*, Examples 7-12. Various test tablets having the same composition but made using different tabletting techniques and compression forces were tested for tensile strength (Sherwood at col. 17, lines 3-13). Each of the test tablets contains about (i) 70% MCC or 70% silicified MCC, and (ii) 30% drug (acetaminophen). Figure 2 shows that the silicified MCC containing tablets (Examples 10-12) have superior tensile strength over the conventional MCC containing tablets at the same compression force.

2. The Examiner's Rejection is Erroneous

According to the Examiner, it would have been obvious to replace Shimizu's MCC with Sherwood's silicified MCC and furthermore: (a) to use the silicified MCC in an amount of 50% as allegedly taught by Shimizu (for MCC) and/or in an amount of 70% as taught by Sherwood; and (b) to achieve oral disintegration in 1-15 seconds as per the presently claimed invention. But the Examiner's position is unfounded.

The combination of Shimizu and Sherwood fails to suggest the formation of a tablet having at least 50% silicified MCC. Shimizu suggests that as much as 50% of the additive component, not 50% of the total tablet weight, can be MCC. The fine granules, which contain the active ingredient, are a substantial proportion of the Shimizu tablet, leaving the maximum suggested amount of MCC to be less than the claimed 50%; e.g., Shimizu maximum of approximately 26-31% MCC. Moreover, modifying a Shimizu tablet to contain at least 50% silicified MCC would not be reasonably expected to exhibit oral disintegration within 1-15 seconds as per the present invention. Shimizu's exemplified tablets do not achieve this oral disintegration speed. Increasing the content of the binder MCC (silicified or not) in the additive component would displace Shimizu's oral disintegrant additive, i.e., sugar alcohol. Using more binder, especially beyond that which Shimizu suggests, and thus less oral disintegrant would be reasonably expected to increase the disintegration time of Shimizu's tablets -- not reduce it to the claimed speed of 1-15 seconds. In short, the applied art neither suggests forming a tablet having the claimed proportions nor does it provide a reasonable expectation of success. These twin errors are explained in greater detail below

(a). No Suggestion of the Claimed "at least 50%"

The Examiner proposes two pathways to find a suggestion of the applicants' claimed "at least 50%" silicified MCC. Most directly, the Examiner relies on Shimizu's supposed teaching of using 3-50% of MCC as overlapping with the claimed at least 50% limitation. But this proposition is factually in error. Shimizu's percentage of MCC refers to the proportion of MCC in the additive portion, only, of the tablet. That is, the MCC can be 50% of the tablet weight ***apart from the fine granules*** (Shimizu at col. 10, lines

25-29 (emphasis added)). Thus, even using Shimizu's maximum amount of 50% MCC, when the amount of the fine granules are added to the equation, the amount of MCC is necessarily *less than 50%* relative to the total tablet weight.

More importantly, the weight of the fine granules is a significant part of the total tablet weight. Indeed, the fine granules contain the active ingredient or drug. The examples in Shimizu show that generally about 40-50% of the tablet is comprised of these drug-containing fine granules (specifically 38% (Example 3) to 47-48% (Examples 4-8) of fine granules). Of the 50-60% remainder, Shimizu teaches that at most half could be MCC. As a percentage of the total tablet weight, the maximum amount of MCC reasonably suggested in Shimizu is only approximately 25-30%.

Having misunderstood the basis for the "50%" MCC disclosed in Shimizu, the Examiner's rationale is fatally flawed. The range of MCC content taught in Shimizu does not overlap with, abut, or fairly suggest the claimed "at least 50%" silicified MCC. Shimizu does not present a range of operable concentrations from which applicants' claimed range could have been selected, as the Examiner seems to portend. To the contrary, the Shimizu range does not overlap, and is necessarily separate from and less than, the claimed range. Because the maximum amount of MCC allowed in Shimizu is necessarily less than 50% of the total tablet weight and in reality is much less, e.g. 25-30% max., Shimizu does not teach or suggest the applicants' claimed higher amounts of "at least 50%" silicified MCC.

The Examiner's second rationale for attaining the claimed "at least 50%" silicified MCC is based on the teachings in the secondary reference, Sherwood. Per the Examiner, the average artisan would have found it obvious to replace the MCC of

Shimizu with silicified MCC and to use considerably more of the binder/diluent as shown in Sherwood Examples 10-12 (namely 70%). But, the Examiner fails to address why the average artisan would modify the proportion of "additives" in Shimizu's orally disintegratable tablet based on Sherwood's test tablets and in contradiction of the other teachings in Sherwood.

Sherwood teaches that MCC is generally used in an amount of 5-30% or more (Sherwood at col. 7, lines 48-51). This range is consistent with Shimizu's effective teaching of maximum MCC content of around 30% and its practical application of 5-12%. Yet Sherwood teaches that when replacing MCC with silicified MCC, the amounts can be decreased due to the latter's better compressibility (compare Sherwood col. 3 lines 23-40; and col. 12, lines 9-13). The advantage of silicified MCC is in its superior compressibility and the concomitant ability to use less -- not more -- of the binder/diluent. Contrary to the Examiner's desire, the worker skilled in the art would have been led to use the same or less amount of silicified MCC when modifying an MCC-containing tablet.

The test tablets in Examples 10-12 of Sherwood do not rescue the Examiner's position. The 70% silicified MCC tablets, which are not described as being orally disintegrating, are not combineable with the teachings in Shimizu for obtaining an orally disintegratable tablet. Applying the test tablet proportions creates irreconcilable conflicts with the Shimizu orally disintegratable tablet teaching. For example, 100% of the "additive" in the test tablets is silicified MCC whereas Shimizu teaches that MCC is restricted to only 50% of the "additive." Exceeding the Shimizu limit on the amount of MCC would come at the expense of the Shimizu orally disintegrating excipient of sugar

alcohol. Importantly, nowhere does Sherwood (or Shimizu) suggest that silicified MCC has orally disintegrating properties such that it could replace sugar alcohol. The fact that Sherwood can use more silicified MCC than Shimizu is irrelevant given that Sherwood is not limited to (or even addressing) orally disintegrating tablets. And the extreme tablets of Sherwood Examples 7-12 are less relevant because they are not conventional pharmaceutical formulations but rather test tablets designed to highlight/amplify the difference in compressibility between MCC and silicified MCC. Thus, the test tablets do not have a lubricant, disintegrant, etc., as is customarily found in an oral dosage form. Similarly, the amount of MCC and silicified MCC is extreme based on Sherwood's own description of "typical" amounts of MCC being 5-30% (See col. 7, lines 48-51). The isolated teaching in the experimental tablets of Sherwood would not have been understood by the worker of ordinary skill in the art as a basis to override the proportions taught in Shimizu for achieving an orally disintegrating tablet.

The conflict also arises on the amount of active. While Sherwood uses 30% active in Examples 7-12, Shimizu supplied active as fine granules of which at least 10% is active. To arrive at 30% active would require more than 30% of fine granules. But that would leave insufficient room for 70% silicified MCC. The proportions taught in Sherwood Examples 7-12 cannot be translated into the Shimizu orally disintegrating tablet scheme, nor is there any reason to apply them.

Accordingly neither Shimizu nor Sherwood suggests the use of at least 50% silicified MCC in making an orally disintegrating tablet. In the absence of such a suggestion the Examiner's rejection is improper.

(b). No Reasonable Expectation of 1-15 Second Oral Disintegration

Even if Shimizu and Sherwood are combined as sought by the Examiner, the resulting tablet would not be reasonably expected to exhibit the claimed 1-15 second oral disintegration. Shimizu does not place the worker of ordinary skill in the art in possession of a tablet that is orally disintegratable in 15 seconds or less. Although Shimizu generically describes an oral disintegration time of "more preferably about 30 seconds or less" (col. 12, lines 42-47), the fastest working example achieves oral disintegration in 20 seconds (Example 4) – 25% slower than applicants' slowest disintegration time of 15 seconds. And Shimizu's disintegration times were measured as the "[t]ime for complete disintegration only by saliva in the oral cavity" (col. 19, lines 9-11). In contrast, the claim term "orally disintegratable" is expressly defined by applicants as being "measured by the *in vitro* test as described in US Pharmacopoedia 701, without disks" (see the present specification at p. 6, lines 16-18) and generally such test times are somewhat longer than the orally experienced time for disintegration. Thus, Shimizu's tablets if tested in applicant's defined *in vitro* disintegration test would likely yield even longer disintegration times than as reported in Shimizu. Bottom line: Shimizu does not achieve a tablet that orally disintegrates in 15 seconds or less.

Despite this failing, the Examiner proposes that Shimizu's tablets would disintegrate faster if the oral disintegrating excipient was reduced or removed. That is, the average artisan would have been motivated to increase the amount of binder (MCC or silicified MCC) and thus reduce the amount of oral disintegrant (sugar alcohol) with the expectation of increasing the speed of oral disintegration. But reducing the amount of a functional excipient with the expectation of increasing its function is not reasonable.

The Examiner counters that the use of silicified MCC would have been expected to increase disintegration speed as evidenced by the present claims (Final OA at page 3, lines 15-16)." But the present claims are not part of the prior art nor described in Sherwood. The Examiner's position is based on improper hindsight reconstruction as she seeks to use the applicants' discoveries and disclosures against them. Of course, such is forbidden under 35 U.S.C. § 103.

The Examiner also contends that Sherwood teaches silicified MCC has superior disintegration over MCC. Not true! The Examiner's citation to column 2, line 46, of Sherwood is a description of conventional and commercially available MCC as having "superior compressibility and disintegration properties." This passage is not even referring to silicified MCC. The Examiner's other citation (col. 4, lines 50-51) recites an object of the invention as including "acceptable disintegration properties" - not superior disintegration properties over MCC. The property that Sherwood trumpets as being superior in silicified MCC over MCC is compressibility: see col. 4, lines 40, 44, and 54; col. 6, lines 13-14, 20, and 26-30; col. 9 lines 1-6; etc. Disintegration is not taught in Sherwood as being improved by the use of silicified MCC.

Moreover, the "acceptable" disintegration property mentioned in Sherwood is not oral disintegration but rather the convention pharmaceutical disintegration that occurs in the gastrointestinal tract. The difference between the two is well known. For example, a typical aspirin tablet will certainly disintegrate relatively quickly in a patient's stomach, but does not disintegrate in the patient's mouth in, e.g., 15 seconds or less. Sherwood is referring to the usual disintegration in the stomach; e.g., "excellent disintegration and dissolution properties when exposed, e.g., to gastrointestinal fluid" (Sherwood col. 4,

lines 65-67). There is no teaching in Sherwood of achieving oral disintegration properties by the use of silicified MCC (or MCC in general). As described in pages 1-3 of the present specification, oral disintegration in the prior art required special excipients and not mere gastrointestinal disintegrants.[3] Accordingly, Sherwood:

- does not teach that silicified MCC has superior disintegration over MCC; and
- does not teach that MCC or silicified MCC has oral disintegration properties.

Therefore, in the absence of any teaching in the applied art that silicified MCC could provide oral disintegration properties, the average artisan would not have had a reasonable expectation of obtaining a tablet that orally disintegrates in 1-15 seconds by replacing the known oral disintegrant (sugar alcohol) in Shimizu with the binder/diluent (silicified MCC) of Sherwood.

The Examiner's rejection fails both requirements for establishing a prima facie case of obviousness. The Examiner has failed to provide any teaching, suggestion, or motivation to use the claimed higher amounts of silicified MCC and the Examiner has failed to show that such a higher amount would have been reasonably expected to achieve the claimed rapid oral disintegration. To the contrary, the applied art leads away from the claimed amounts and expects such a modification to increase the oral disintegration time instead of reducing it. The rejection fails to establish a prima facie case of obviousness and reversal thereof is requested.

[3] Indeed, conventional disintegrants can be additionally present in some embodiments of the present invention as described on page 8 of the Specification, which further confirms the difference between an oral disintegrant and a conventional disintegrant.

3. Other Independent Claims and Their Dependent Claims

The Examiner's rejection does not separately discuss the various independent claims. While the above arguments apply equally well to all the claims, applicants wish to point out some further distinctions.

Independent claim 30 recites an orally disintegratable tablet "consisting essentially of" 50-90% silicified MCC, 0-20% low substituted HPC, a lubricant, and an active agent, wherein the tablet exhibits disintegration within 1-15 seconds *in vitro*. The semi-closed transitional phrase "consisting essentially of" limits the scope of claim 30 to the recited ingredients and those that do not materially affect the basic and novel properties of the claimed tablet. See *In re Hertz*, 537 F.2d 549, 551-552 (CCPA 1976); *PPG Indus. v. Guardian Indus. Corp.*, 156, F.3d 1351, 1355 (Fed. Cir. 1998). The formation of this tablet was not addressed by Examiner's rejection. Additionally, Sherwood Examples 7-12 do not contain a lubricant.

Independent claim 32 recites a process of rapidly releasing active agent from a solid tablet, which comprises disintegrating a tablet comprising at least 50% of a matrix of silicified MCC (and the active) by placing the tablet in a water environment for 1-15 seconds. Sherwood does not teach or suggest such a process.

Independent claim 34 is a Jepson claim that recites improving an orally disintegrating tablet by providing a matrix of silicified MCC in an amount of at least 50% within the tablet. Neither Shimizu nor Sherwood teaches that a matrix of at least 50% silicified MCC could be used to improve the oral disintegration properties of an orally disintegratable tablet. Indeed, Sherwood does not mention such tablets and thus could not render such an improvement obvious.

Reversal of the Examiner's rejection is requested.

B. §103(a) Rejection over Betzing in view of Shimizu and Sherwood

Claims 1, 5, 7-9, and 11-37 stand rejected as being unpatentable under 35 U.S.C. §103(a) over Betzing et al., U.S. Patent No. 5,776,492 (hereinafter "Betzing") in view of Shimizu and Sherwood. This rejection fails to establish a prima facie case of obviousness and reversal thereof is requested.

1. The Applied Art

Shimizu and Sherwood are discussed above.

Betzing is directed to tablets of tramadol or a tramadol salt which rapidly disintegrate in water "so that a suspension is available which contains the active ingredient and which can be drunk immediately" (Betzing at col. 2, lines 40-43). The tablets are described as "binder-free" tablets comprising MCC and the tramadol in a weight ratio of at least 2:1 (Betzing at col. 2, lines 46-54). Such tablets "when they are taken ... make use of the positive properties of a liquid form of medication" (Betzing at col. 3, lines 3-6). No mention is made of applicants' claimed silicified microcrystalline cellulose. Betzing does not describe the tablets as orally disintegrating tablets.

Betzing's working examples 1-5 are directed to tablets containing tramadol and MCC, and examples 2-5 further contain starch. The MCC was present in amounts ranging from 43.78 to 74 weight % relative to the total weight of the tablets. Comparative examples 6 and 7 replaced MCC with either "water-soluble lactose" (example 6) or "insoluble calcium hydrogen phosphate" (example 7). Each of the tablets was placed in 600 mL of gastric juice with a pH of 1.2, and disintegration times were

measured (Betzing col. 5, lines 11-16). The disintegration times for the working examples ranged from "25-30 sec" up to "110 sec" (Betzing at Table in col. 7). The disintegration time for the lactose-substituted comparative example was "> 10 min;" the disintegration time for the calcium hydrogen phosphate-substituted comparative example was "360 sec" (Betzing at Table in col. 7).

2. The Examiner's Rejection is Erroneous

According to the Examiner, Betzing discloses a rapidly disintegrating tablet containing MCC and tramadol in a ratio of at least 2:1. Betzing differs from the claimed invention because (i) it fails to teach silicified MCC and (ii) it fails to teach that the tablet is orally disintegratable. Nonetheless, the Examiner finds that it would have been obvious to substitute the MCC of Betzing with Sherwood's silicified MCC and to prepare the tablet as an orally disintegrating tablet in view of Shimizu's teaching of the desirability of the same. This rejection is in error as failing to have proper motivation or a reasonable expectation of success.

Betzing discloses a specific combination of active ingredient (tramadol) and excipients (MCC and optionally starch) in set ratio ranges. More importantly, Betzing teaches that any modification of the excipients reduces the speed of the disintegration. Thus, far from inviting the use of any binder or diluent, Betzing is strictly limited to the precise excipients named therein. In such a circumstance, it is unknown why a worker skilled in the art would have found it obvious to modify the Betzing unique combination of excipients to use a different excipient, namely Sherwood's silicified MCC.

For example, if the proportion of MCC to tramadol and starch is less than 2:1:1, "the disintegration rate of the tablets decreases considerably" (Betzing at col. 3, lines 20-25). Replacing the MCC with a water-soluble sugar or water- insoluble calcium hydrogen phosphate "results in a significant decrease in disintegration rate" (Betzing at col. 3, lines 25-28). Indeed, Betzing's comparative examples 6 and 7 replaced MCC with "water-soluble lactose" (example 6) and "insoluble calcium hydrogen phosphate" (example 7) and resulted in disintegration times of "> 10 min" and "360 sec" respectively (Betzing at Table in col. 7); much slower than the 25-110 seconds for the MCC-containing working examples (Betzing at Table in col. 7). Betzing therefore counsels against modifying the precise combination of excipients disclosed therein.

Sherwood dose not overcome the narrow and specific teachings of Betzing. Replacing MCC with a lesser amount of silicified MCC, one of the advantages flowing from superior compressibility taught in Sherwood, would be contrary to Betzing's required ratio ranges. Betzing does not desire to use less MCC. Nor is compressibility a problem in Betzing as a hardness in the range of 80 to 100N is achieved (col. 3, lines 10-12). In short, Betzing leads the worker skilled in the art away from modifying or replacing any excipient and Sherwood fails to suggest a reason to nonetheless modify Betzing. The Examiner's rejection fails to provide a reason or motivation to modify Betzing, other than to reconstruct the claimed composition. Such hindsight reconstruction is improper.

Separately the Examiner's rejection fails to establish a reasonable expectation of success in attaining an orally disintegrating tablet that meets the claimed disintegration speed of 1-15 seconds. The fastest disintegration time achieved by Betzing was 25-30

seconds. Sherwood does not relate to or disclose an orally disintegration tablet and Shimizu's fastest tablets took 20 seconds in saliva to disintegrate. Although none of the applied teachings can achieve oral disintegration in 1-15 seconds, the Examiner nonetheless summarily concludes that it would have been obvious to attain such speed. As explained in the response to the previous rejection, Sherwood does not teach or suggest that silicified MCC improves oral disintegration over MCC. Accordingly, the combination of references does not provide a reasonable expectation of successfully decreasing the oral disintegration time to within the claimed range.

The lack of a reasonable expectation of success is further supported by the Examiner's reliance on Shimizu for the desirability of the claimed disintegration times. The Examiner cites Shimizu but does not explain how Betzing would be modified by Shimizu in order to achieve the claimed speed. A review of Shimizu, however, confirms the error in the Examiner's position. Shimizu teaches the use of a water-soluble sugar as the basic agent for achieving oral disintegration (Shimizu at col. 10, lines 1-6). In contrast, Betzing discloses that lactose, a water-soluble sugar, "results in a significant decrease in disintegration rate" (Betzing at col. 3, lines 25-28). Accordingly, the proposition that Shimizu could be combined with Betzing to obviously obtain the claimed 1-15 second oral disintegration time is refuted by the express teaching in Betzing itself. The Examiner has failed to provide any basis to expect that Betzing could be converted into an orally disintegratable tablet as per the present claims. In the absence of a reasonable expectation of success, the Examiner's rejection is in error.

In summary, the worker of ordinary skill in the art would not have been motivated to modify Betzing in view of Shimizu and Sherwood to contain at least 50% silicified

microcrystalline cellulose, and would not have reasonably expected such a hypothetical tablet to be orally disintegratable in 1 to 15 seconds. Accordingly, the Examiner has failed to establish a prima facie case of obviousness, and reversal of this rejection is requested.

3. Other Independent Claims and Their Dependent Claims

As in the previous rejection, the Examiner again fails to separately discuss the various independent claims. While the above traversal is sufficient to show the unobviousness of all claims, the additional distinctions mentioned above for independent claims 30, 32, and 34 are incorporated herein.

Reversal of the Examiner's rejection is requested.

VIII. Conclusion

For the reasons set forth above, each of the Examiner's rejections is in error and reversal thereof is respectfully requested.

Please charge the required Appeal Brief filing fee in the amount of $510.00 to Deposit Account No. 50-2877.

Respectfully submitted,

Date: 8/1/2008

By: _____
Mark R. Buscher
Reg. No. 35,006

Philip A. Caramanica, Jr.
Reg. No. 51,528

7130 Heritage Village Plaza
Suite 202
Gainesville, VA 20155
703 753 5256

Claims Appendix

1. (Previously Presented) A tablet for oral administration, comprising an effective amount of an active agent and at least 50% silicified microcrystalline cellulose, wherein said tablet is orally disintegratable within the range of 1 to 15 seconds.
2. (Canceled)
3. (Canceled)
4. (Canceled)
5. (Previously Presented) The tablet according to claim 1, wherein said tablet exhibits oral disintegratability in not less than 2 seconds.
6. (Canceled)
7. (Original) The tablet according to claim 1, wherein said silicified microcrystalline cellulose is contained in an amount within the range of 55% to 90%.
8. (Original) The tablet according to claim 7, wherein said silicified microcrystalline cellulose is contained in an amount within the range of 60% to 80%.
9. (Original) The tablet according to claim 1, wherein said active agent and said silicified microcrystalline cellulose together represent at least 80% of the tablet weight.
10. (Canceled)
11. (Original) The tablet according to claim 1, wherein said silicified microcrystalline cellulose contains 1-5% silicon dioxide.

12. (Original) The tablet according to claim 1, wherein said silicified microcrystalline cellulose has an average particle size within the range of 20-200 microns.

13. (Original) The tablet according to claim 12, wherein the median particle size is about 90 microns.

14. (Original) The tablet according to claim 1, which further comprises a disintegrant.

15. (Original) The tablet according to claim 14, wherein said disintegrant is selected from the group consisting of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, crosscarmellose sodium, crosspovidone, starch, and combinations thereof.

16. (Original) The tablet according to claim 15, wherein said disintegrant is low substituted hydroxypropyl cellulose.

17. (Original) The tablet according to claim 14, wherein said disintegrant is contained in an amount of 0.5% to 20%.

18. (Original) The tablet according to claim 1, which does not contain an effervescent excipient.

19. (Original) The tablet according to claim 1, which has a hardness of 20N to 40N.

20. (Original) The tablet according to claim 1, which has a friability of less than 1%.

21. (Original) The tablet according to claim 1, wherein said tablet does not contain a water soluble binder.

22. (Original) The tablet according to claim 1, which further comprises at least one additional excipient selected from the group consisting of taste masking agents, sweeteners, lubricants, stabilizers, preservatives, and pH-adjustors.

23. (Original) The tablet according to claim 1, wherein said active agent is selected from the group consisting of pharmaceutical active agents, nutrients, nutraceuticals, and cosmetics.

24. (Original) The tablet according to claim 23, wherein said active agent is one or more vitamins.

25. (Original) The tablet according to claim 23, wherein said active agent is a pharmaceutically active agent.

26. (Original) The tablet according to claim 25, wherein said pharmaceutically active agent is present in the form of coated particles containing said pharmaceutically active agent.

27. (Original) The tablet according to claim 26, wherein said coating is an extended release or an enteric coating.

28. (Original) The tablet according to claim 25, wherein said pharmaceutically active agent is selected from the group consisting of anti-inflammatories, antirheumatics, antiemetics, analgetics, antiepileptics, antipsychotics, antidepressants, hypnotics, antiulcerics, prokinetic, antiasthmatics, anti-parkinsonics, cardiovasculars, vasodilators, urologics, hypolipidemics, antidiabetics, and antihistaminics.

29. (Original) The tablet according to claim 25, wherein said pharmaceutically active agent is selected from the group consisting of ibuprofen, acetaminophen, piroxicam, leflunomide, ondansetron, granisetron, paracetamol, carbamazepin,

lamotrigine, clozapine, olanzapine, risperidone, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, zopiclon, zolpidem, cimetidine, ranitidine, omeprazole, metoclopramide, cisapride, domperidon, zafirlukast, montelukast, pramipexole, donepezil, selegiline, zolpidem, zopiclon, doxazosin, terazosin, atenolol, bisoprolol, amlodipine, nifedipine, diltiazem, enalapril, captopril, ramipril, losartan, glyceroltrinitrate, alfuzosin, finasteride, pravastatin, atorvastatin, simvastatin, gemfibrozil, pioglitazone, metformin, terfenadine, loratadine, celecoxib, rofecoxib, and rivastigmine.

30. (Original) A pharmaceutical orally disintegratable tablet which consists essentially of 50% to 90% silicified microcrystalline cellulose, 0% to 20% of low substituted hydroxypropyl cellulose, a lubricant, and an effective amount of a pharmaceutically active agent, wherein said tablet exhibits disintegration within 1 to 15 seconds when tested in an *in vitro* disintegration test.

31. (Original) The pharmaceutical tablet according to claim 30, wherein said tablet further comprises flavorants, colorants, or both.

32. (Previously Presented) A process of rapidly releasing an active agent from a solid tablet, which comprises disintegrating a tablet, which comprises at least 50% of a matrix of silicified microcrystalline cellulose and an effective amount of an active agent, by placing the tablet in a water environment for 1 to 15 seconds.

33. (Previously Presented) The process according to claim 32, wherein said water environment is a water-filled container.

34. (Previously Presented) In an orally disintegrating tablet which disintegrates in 15 seconds or less and which comprises an active agent, the improvement of which

comprises providing a matrix of silicified microcrystalline cellulose in an amount of at least 50% within the tablet.

35. (Original) The orally disintegrating tablet according to claim 34, which does not contain a water soluble binder.

36. (Previously Presented) The tablet according to claim 1, wherein said tablet exhibits oral disintegratability within the range of 1 to 10 seconds.

37. (Previously Presented) The tablet according to claim 1, wherein said tablet exhibits oral disintegratability within the range of 1 to 2 seconds.

Evidence Appendix

(NONE)

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Related Proceedings Appendix

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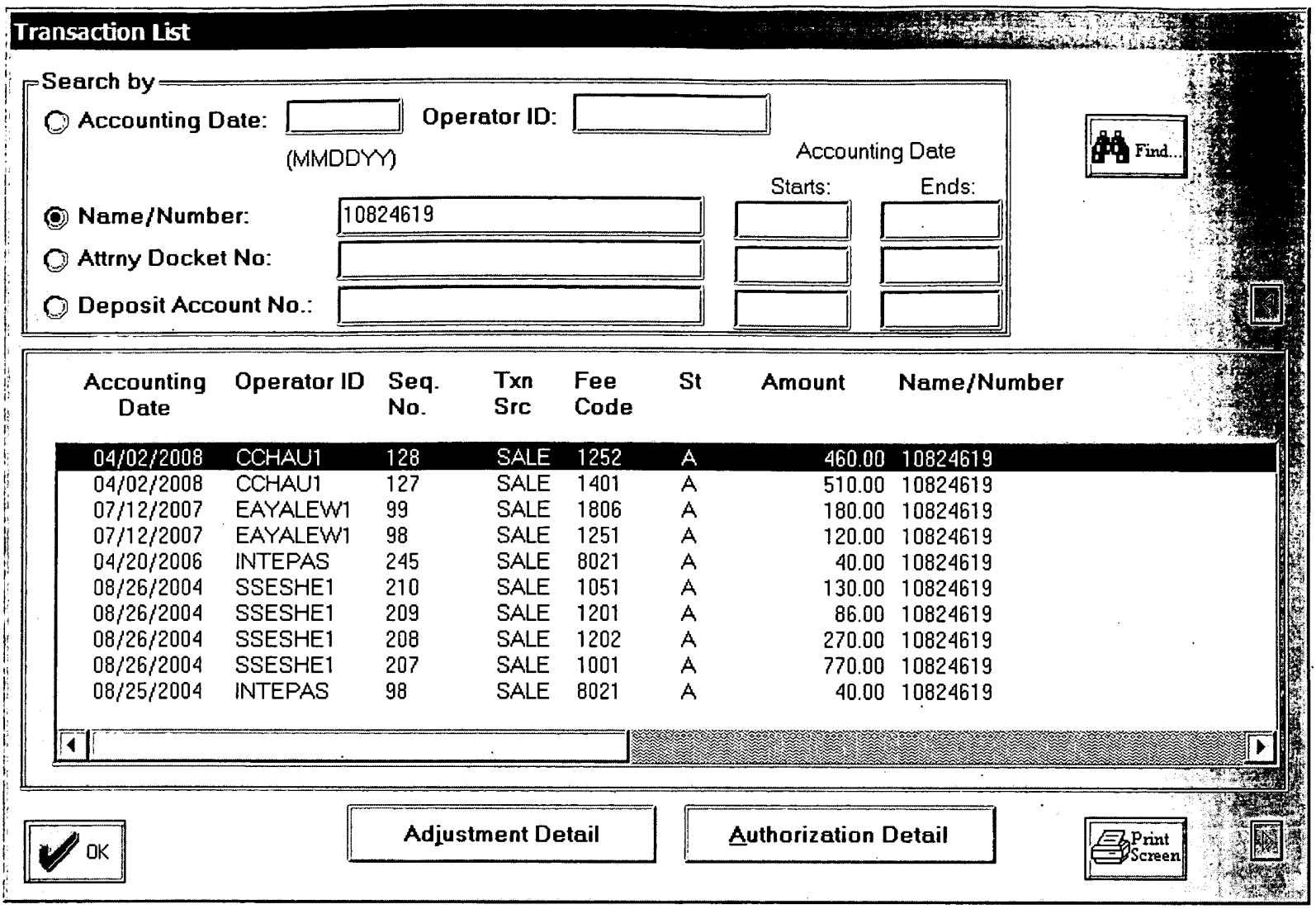
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